

# Kinetic resolution of alkyne-substituted quaternary oxindoles via copper catalysed azide-alkyne cycloadditions

Brittain, William D G; Buckley, Benjamin R; Fossey, John S

DOI:

[10.1039/C5CC04886A](https://doi.org/10.1039/C5CC04886A)

License:

Creative Commons: Attribution (CC BY)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Brittain, WDG, Buckley, BR & Fossey, JS 2015, 'Kinetic resolution of alkyne-substituted quaternary oxindoles via copper catalysed azide-alkyne cycloadditions', *Chemical Communications*, vol. 51, no. 97, pp. 17217-17220.  
<https://doi.org/10.1039/C5CC04886A>

[Link to publication on Research at Birmingham portal](#)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

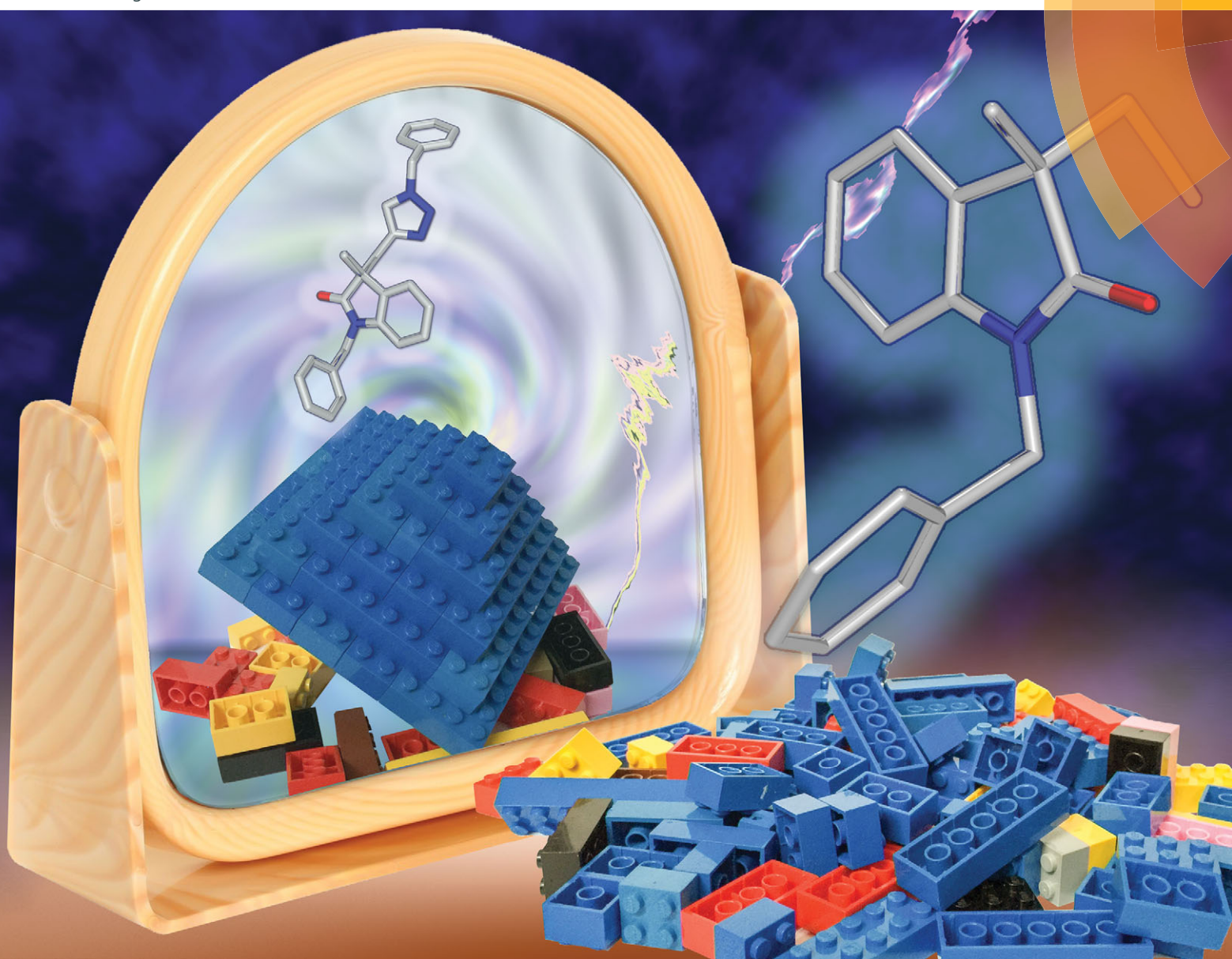
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

# ChemComm

Chemical Communications

[www.rsc.org/chemcomm](http://www.rsc.org/chemcomm)



ISSN 1359-7345



## COMMUNICATION

Benjamin R. Buckley, John S. Fossey *et al.*  
Kinetic resolution of alkyne-substituted quaternary oxindoles *via* copper catalysed azide-alkyne cycloadditions



Cite this: *Chem. Commun.*, 2015, 51, 17217

Received 12th June 2015,  
Accepted 12th August 2015

DOI: 10.1039/c5cc04886a

www.rsc.org/chemcomm

## Kinetic resolution of alkyne-substituted quaternary oxindoles *via* copper catalysed azide–alkyne cycloadditions†

William D. G. Brittain,<sup>a</sup> Benjamin R. Buckley<sup>‡\*b</sup> and John S. Fossey<sup>‡\*a</sup>

**The synthesis and kinetic resolution of quaternary oxindoles through copper catalysed azide–alkyne cycloadditions is presented. Selectivity factors (*s*) up to  $22.1 \pm 0.5$  are reported. Enantioenriched alkynes and triazoles were obtained in  $\geq 80\%$  enantiomeric excess (e.e.).**

Click chemistry was first outlined in 2001 by K. B. Sharpless and co-workers, the copper catalysed azide alkyne cycloaddition (CuAAC) has lived up to Sharpless' accolade as "the cream of the crop" in this area.<sup>1</sup> The CuAAC reaction predictably delivers 1,4 substituted triazoles in good yields, from the reaction of terminal alkynes with organic azides in the presence of a Cu(I) catalyst. Despite the ubiquity of the CuAAC reaction there are relatively few reports of asymmetric variants.<sup>2</sup> Yet enantioenriched triazoles and alkynes are potentially important in many areas of chemistry and biology.<sup>3</sup>

Kinetic resolution (KR) of a racemic mixture takes advantage of a difference in the rate of the reaction of either enantiomer through diastereomeric interactions.<sup>4</sup> Fu and co-workers have championed non-enzymatic catalytic methods for the KR of secondary alcohols and other substrates.<sup>5</sup> In this area recent advances have built on Fu's findings and resolution of chiral alcohols is a relatively mature field.<sup>6</sup> A particular advantage of KR is that it is possible to obtain high e.e.s of both unreacted starting materials and products dependent upon the selectivity factor (*s*) and the conversion. Kagan showed that for a given KR it is relatively straight forwards to relate conversion and starting material e.e. to selectivity factor. KR of chiral alkynes or azides through triazole formation is one strategy open to exploitation to access enantioenriched triazoles and starting materials,

thus enabling recovery of non-racemic alkynes which could be further derivatised.

To the best of our knowledge there are no reports of successful KRs of alkynes *via* the CuAAC reaction. Kinetic resolution of terminal alkynes is therefore of importance to the overall development of stereoselective click chemistry. Research into asymmetric click methodology thus far has been mainly focused on desymmetrisation and only a single successful report on KR (of azides) has been published.

Resolution of racemic azides *via* the CuAAC reaction has been achieved by Meng *et al.*<sup>7</sup> using a Cu–PyBox catalyst,<sup>8</sup> selectivity factors (*s*) up to *s* = 8 were obtained.<sup>9</sup> Meng *et al.* were unable to kinetically resolve racemic terminal alkynes (*s* = 1).<sup>7</sup> A range of five different terminal alkynes were tested and no enantiomeric discrimination was observed whatsoever with any compounds tried. They accounted for this observation using a mononuclear transition state model. However, more recently evidence has emerged that Cu–PyBox systems might not always follow a mononuclear arrangement. Panera *et al.* reported X-ray crystal structures of binuclear phenyl and isopropyl PyBOX copper(I) chloride complexes, and used these solid state structures to rationalise the stereochemical outcome of their asymmetric catalytic synthesis of propargylamines.<sup>14</sup> It struck us that this binuclear PyBox model could have synergy with the binuclear model for the CuAAC, proposed by Fokin *et al.*<sup>15</sup> and Kuang *et al.*<sup>16</sup> Work by Jin *et al.* and Makarem *et al.* has provided strong evidence to support this catalytic model with stable dinuclear copper acetylide intermediates being successfully crystallised.<sup>17</sup>

Our team has a long-standing interest in quaternary oxindoles,<sup>18</sup> and a relevant report on desymmetrisation,<sup>2a</sup> prompted us to begin investigation of their potential as substrates for catalytic kinetic resolution. Oxindole derivatives (Fig. 1) can possess potent biological activity as calcium channel blockers,<sup>19</sup> anti-angiogenics,<sup>20</sup> antitumor agents<sup>21</sup> and analgesics.<sup>19,22</sup> For example, the antitumor agent **I**, the natural products donaxaridine **II**, dioxibrassinine **III** and the popular natural product target gelsamine **IV** (Fig. 1). Therefore, efficient access to nonracemic quaternary oxindoles is of considerable interest to the

<sup>a</sup> School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK. E-mail: j.s.fossey@bham.ac.uk

<sup>b</sup> Department of Chemistry, Loughborough University, Loughborough, Leicestershire, LE11 3TU, UK. E-mail: b.r.buckley@lboro.ac.uk

† Electronic supplementary information (ESI) available: Experimental procedures, HPLC traces, NMR data and detailed screening tables. See DOI: 10.1039/c5cc04886a

‡ The project was conceived equally by JSF and BRB. Experiments were performed at the University of Birmingham hence JSF is corresponding author for experimental details, but both BRB and JSF may be contacted about this manuscript.



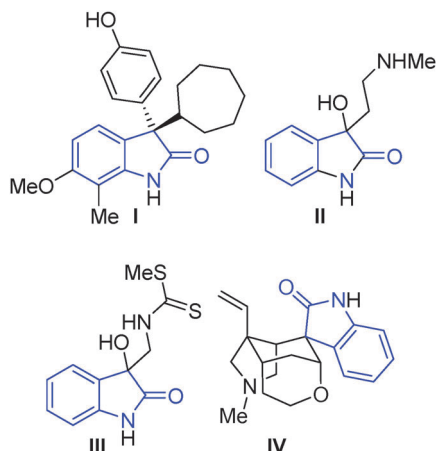


Fig. 1 Exemplar biologically active quaternary C-3 oxindoles; I: antitumor agent;<sup>10</sup> II: donaxaridine;<sup>11</sup> III: dioxibassinine;<sup>12</sup> IV: gelsemine.<sup>13</sup>

medicinal chemistry<sup>23</sup> and veterinary science<sup>24</sup> communities. Not only is access to non-racemic triazoles of interest but access to high e.e. alkynes is of importance. Access to enantioenriched all carbon quaternary stereogenic centres bearing alkyne functionality is demanding,<sup>25</sup> and alkynes are a versatile synthetic handle capable of undergoing a diverse array of transformations.<sup>26</sup> Access to enantioenriched alkynes therefore could lead to a plethora of stereocontrolled derivatives. In order to test whether kinetic resolution of alkyne appended quaternary oxindoles is possible (generically represented in Scheme 1a) we prepared compound **1**. Propargylation of 3-methyl-2-oxindole (see ESI†), followed by *N*-benzylation gave racemic **1** (Scheme 1b), our substrate for KR.

To our delight, an initial probe reaction of racemic **1** with benzyl azide, in acetone under control of a combination of Cu(I)Cl and PhPyBOX (L1) (12.5 and 15 mol% respectively) gave a selectivity of  $s = 5.3$ . Conversion was determined by examination of proton NMR spectrums and e.e. by HPLC analysis (see ESI† for details). Optimisation of the reaction conditions was then explored. A series of readily available copper sources were probed, including Cu(I), Cu(II) and Cu(0) species, under standard conditions of 0.6 equivalents of benzyl azide (3b), 12.5 mol% of copper source and 15 mol% of PhPyBox ligand (L1) at 0 °C for

Table 1 KR of **1** with PhPyBox and various copper sources

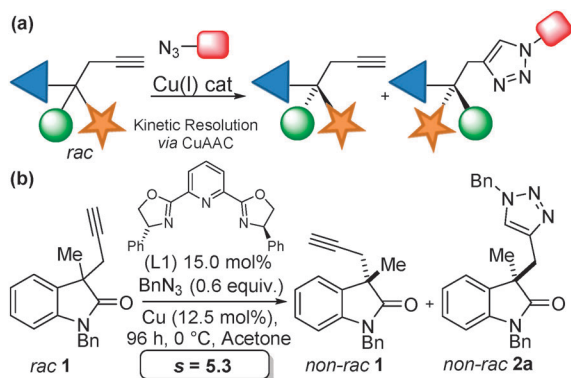
Entry	Copper Source	Conv. <sup>a</sup> (%)	e.e. SM <sup>b</sup> (%)	e.e. 2a <sup>b</sup> (%)	Selectivity factor (s) <sup>c</sup>
1	CuCl	37	34	43	5.3
2	CuBr	14	8	8	3.2
3	CuI	51	26	29	2.1
4	Cu(OTf)-toluene 0.5	10	3	16	1.8
5	Cu(OAc)	0	0	—	—
6	Cu(OAc) <sub>2</sub>	8	4	57	2.8
7	CuSO <sub>4</sub> , NaAsc	13	1	—	—
8	Cu(OTf) <sub>2</sub>	0	0	—	—
9	Cu metal	0	0	—	—

<sup>a</sup> Conversion determined by inspection of <sup>1</sup>H NMR spectra (see ESI).

<sup>b</sup> e.e. of recovered starting material (HPLC). <sup>c</sup>  $s = \ln[(1 - c)(1 - ee)] / \ln[(1 - c)(1 + ee)]$ .

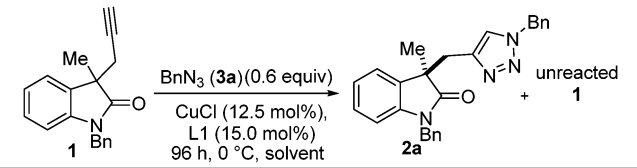
96 h (Table 1). Of copper sources tested, our first choice, Cu(I)Cl was confirmed as the superior choice selectivity factor (Table 1, entry 1). Cu(I)Br gave a lower conversion and selectivity factor (Table 1, entry 2); Cu(I)I offered improved conversion but selectivity factor was again compromised (Table 1, entry 3). Of the other copper sources tried Cu(I)OTf, Cu(II)(OAc)<sub>2</sub> and CuSO<sub>4</sub> combined with NaAsc (Table 1, entries 4, 6 and 7 respectively) gave approximately stoichiometric conversion with respect to catalyst loading. Cu(I)OAc, Cu(II)OTf<sub>2</sub> and Cu(0) NaAsc (Table 1, entries 5, 8 and 9 respectively) did not deliver any triazole-containing products. Increasing the reaction temperature did not improve the reaction outcomes and Cu(I)Cl was selected as the copper source of choice for further optimisation studies.

Next, the choice of solvent was investigated (Table 2), acetone had already been shown to give a promising selectivity and is restated in Table 2 (entry 1) to aid comparison. Surprisingly 2-butanone was ineffective (Table 2, entry) giving no conversion. Since Zhou *et al.* had already reported dicarbonyl containing solvents were effective for a related desymmetrisation reaction we also included this class of solvent in our screening.<sup>2a,27</sup> 2,5-Hexanedione (Table 2, entry 3) gave a huge jump in selectivity factor ( $s = 22.1 \pm 0.5$ ) and good conversion (42%), 2,3-butanedione (Table 2, entry 4) gave poorer conversion and poorer selectivity (34% and  $s = 2.5$  respectively). A mixture of acetone and 2,5-hexanedione (Table 2, entry 5) gave 61% conversion (against 0.6 equiv. of azide, *i.e.* full conversion) but selectivity factor was also poor ( $s = 3.5$ ). THF gave a promising selectivity factor of  $s = 8.7$  (Table 2, entry 6), and all other solvents tried gave inferior results (Table 2, entries 7–12). We speculated that 2,5-hexanedione may be acting as a ligand for copper but use in substoichiometric amounts (equivalent to catalyst loading) had a negative effect on the selectivity. During the course of this optimisation study the order of addition was found to be crucial to obtaining reproducible results. Importantly, the alkyne must be added to a solution of *in situ* formed catalyst at room temperature before cooling to 0 °C (see ESI† for full details).



Scheme 1 (a) General scheme for the CuAAC KR strategy; (b) application of KR to alkynyl C-3 quaternary oxindoles.



Table 2 KR of **1** with PhPyBox, CuCl and various solvents


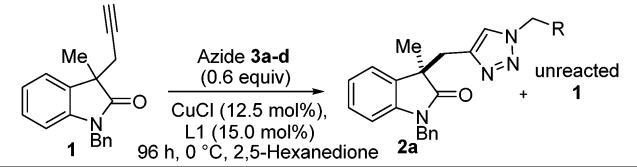
Entry	Solvent	Conv. <sup>a</sup> (%)	e.e. SM <sup>b</sup> (%)	e.e. <b>2a</b> <sup>b</sup> (%)	Selectivity factor ( <i>s</i> ) <sup>c</sup>
1	Acetone	37	34	43	5.3
2	2-Butanone	0	—	—	—
3	<b>2,5-Hexanedione</b>	<b>42</b>	<b>61</b>	<b>65</b>	<b>22.1<sup>d</sup></b>
4	2,3-Butanedione	34	18	70	2.5
5	Acetone : 2,5-hexanedione (10 : 1)	61	53	59	3.5
6	<b>THF</b>	<b>36</b>	<b>40</b>	<b>59</b>	<b>8.7</b>
7	1,4-Dioxane	17	6	20	1.9
8	<sup>t</sup> BuOH	19	0	—	1.0
9	<sup>t</sup> BuOH/H <sub>2</sub> O	13	0	—	1.0
10	H <sub>2</sub> O	6	—	—	—
11	DMSO	44	18	13	1.9
12	Acetonitrile	14	1	13	1.1

<sup>a</sup> Conversion determined by inspection of <sup>1</sup>H NMR spectra (see ESI). <sup>b</sup> e.e. of recovered starting material (HPLC). <sup>c</sup>  $s = \ln[(1 - c)(1 - ee)] / \ln[(1 - c)(1 + ee)]$ . <sup>d</sup> Average of three  $s = 22.1 \pm 0.5$ , best unique case  $s = 23.2$ .

Despite a broad range of alternative chiral ligands being screened, in our hands, it was only PhPyBox that permitted effective KR. Ligand classes screened that were inferior to PhPyBox included other PyBox variants,<sup>28</sup> PhOX ligands,<sup>29</sup> Trost ligands,<sup>30</sup> phosphoramidites,<sup>31</sup> BINAP<sup>32</sup> and BINOL.<sup>33</sup> For full details of ligand screening see ESI.† Further investigation is needed to probe the ligand requirements for this reaction.

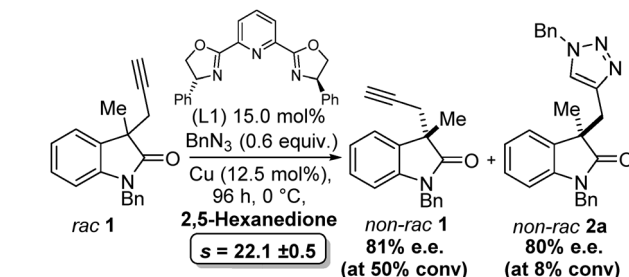
The scope of the benzyl azide was investigated next. Initially we ran experiments using *in situ* prepared azides (from sodium azide and benzyl halide derivatives). Whilst *in situ* preparation of azides offers the advantage of minimising the number of discrete azide manipulations,<sup>34,35</sup> conversions were very poor. So for this communication we prepared just three more isolated benzyl azides to compare against our benchmark reaction (Table 3, entry 1). We probed increasing steric bulk (Table 3, entry 2) by using 2-phenyl benzyl azide (**3b**), conversion was

Table 3 KR using different, isolated, azides



Entry	R	Conv. <sup>a</sup> (%)	e.e. SM <sup>b</sup> (%)	Selectivity factor ( <i>s</i> ) <sup>c</sup>
1	<b>2a</b> C <sub>6</sub> H <sub>5</sub>	46	72	22.1 <sup>d</sup>
2	<b>2b</b> 2-PhC <sub>6</sub> H <sub>4</sub>	45	67	17.5 <sup>e</sup>
3	<b>2c</b> 4-MeC <sub>6</sub> H <sub>4</sub>	46	65	13.1 <sup>f</sup>
4	<b>2d</b> 3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	39	51	11.1 <sup>g</sup>

<sup>a</sup> Conversion determined by inspection of <sup>1</sup>H NMR spectra (see ESI). <sup>b</sup> e.e. of recovered starting material (HPLC). <sup>c</sup>  $s = \ln[(1 - c)(1 - ee)] / \ln[(1 - c)(1 + ee)]$ . <sup>d</sup> See Table 2, entry 3. <sup>e</sup> Average of three  $s = 17.5 \pm 2.0$ , best unique case  $s = 19.8$ . <sup>f</sup> Average of three  $s = 13.1 \pm 1.7$ , best unique case  $s = 14.6$ . <sup>g</sup> Average of three  $s = 11.1 \pm 2.8$ , best unique case  $s = 14.4$ .

Scheme 2 Optimised conditions for the CuAAC kinetic resolution, demonstrating  $\geq 80\%$  e.e. starting material and product can be obtained.

essentially unchanged but selectivity factor dropped a little (albeit it a respectable  $s = 17.5$ ). 4-Methyl benzyl azide (**3c**) and 3,5-trifluoromethyl benzyl azide (**3d**) (Table 3, entries 3 and 4 respectively), offered the chance to judge any effects due to electronic parameters. In both cases similar selectivity factors (13.1 and 11.1) were obtained with a slightly lower conversion when **3d** was used.

Finally, as with any kinetic resolution, by judicious choice of reaction time, and therefore conversion, it is possible to obtain higher e.e. of starting material or product. Indeed, in our case we can obtain  $\geq 80\%$  e.e. of **2a** (albeit at low conversion), see Scheme 2.

These preliminary findings demonstrate that not only is it possible to perform catalytic kinetic resolution with the CuAAC reaction, but selectivity factors greater than 20 are possible Scheme 2. Optimised conditions for the CuAAC kinetic resolution, demonstrating  $\geq 80\%$  e.e. starting material and product can be obtained with biologically relevant substrates. Order of addition, choice of ligand and choice of solvent were key to achieving reproducible results. It was shown that dependant on reaction conversion high e.e. alkynes are recoverable and these could be used for further derivatisation.

Further expansion of substrate scope and detailed mechanistic studies remain to be carried out and we look forward to the opportunity to report on that in due course.

JSF and WDGB would like to thank the University of Birmingham for support. BRB thanks Loughborough University and Research Councils UK for a RCUK Fellowship. Dr Neil Spencer and Dr Chi Tsang are thanked for helpful discussions about NMR spectroscopy and HPLC analysis respectively. WDGB would also like to thank the RSC and the School of Chemistry at the University of Birmingham for travel support facilitating useful discussions *via* the CASE Network.<sup>36</sup> All investigators are grateful for a Royal Society Research Grant (2012/R1) that underpins this project.

## Notes and references

- (a) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021; (b) W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radić, P. R. Carlier, P. Taylor, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 1053–1057.
- (a) F. Zhou, C. Tan, J. Tang, Y.-Y. Zhang, W.-M. Gao, H.-H. Wu, Y.-H. Yu and J. Zhou, *J. Am. Chem. Soc.*, 2013, **135**, 10994–10997; (b) T. Osako and Y. Uozumi, *Org. Lett.*, 2014, **16**, 5866–5869; (c) T. Song, L. Li, W. Zhou, Z.-J. Zheng, Y. Deng, Z. Xu and L.-W. Xu, *Chem. – Eur. J.*, 2015, **21**, 554–558; (d) G. R. Stephenson,



- J. P. Buttress, D. Deschamps, M. Lancelot, J. P. Martin, A. I. G. Sheldon, C. Alayrac, A.-C. Gaumont and P. C. B. Page, *Synlett*, 2013, 2723–2729; (e) Z.-J. Zheng, F. Ye, L.-S. Zheng, K.-F. Yang, G.-Q. Lai and L.-W. Xu, *Chem. – Eur. J.*, 2012, **18**, 14094–14099.
- 3 (a) P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905–4979; (b) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249–1262.
- 4 (a) H. B. Kagan and J. C. Fiaud, *Topics in Stereochemistry*, John Wiley & Sons, Inc., 2007, ch. 4, pp. 249–330, DOI: 10.1002/9780470147276; (b) J. M. Goodman, A.-K. Köhler and S. C. M. Alderton, *Tetrahedron Lett.*, 1999, **40**, 8715–8718.
- 5 (a) K. Tanaka and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 8078–8079; (b) B. Tao, J. C. Ruble, D. A. Hoic and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 5091–5092; (c) J. C. Ruble, H. A. Latham and G. C. Fu, *J. Am. Chem. Soc.*, 1997, **119**, 1492–1493; (d) G. C. Fu, *Acc. Chem. Res.*, 2000, **33**, 412–420; (e) G. C. Fu, *Acc. Chem. Res.*, 2004, **37**, 542–547.
- 6 (a) X. Li, P. Liu, K. N. Houk and V. B. Birman, *J. Am. Chem. Soc.*, 2008, **130**, 13836–13837; (b) B. Hu, M. Meng, Z. Wang, W. Du, J. S. Fossey, X. Hu and W.-P. Deng, *J. Am. Chem. Soc.*, 2010, **132**, 17041–17044; (c) S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann and E. M. Ruel, *J. Am. Chem. Soc.*, 1998, **120**, 1629–1630; (d) D. Belmessieri, C. Joannesse, P. A. Woods, C. MacGregor, C. Jones, C. D. Campbell, C. P. Johnston, N. Duguet, C. Concellon, R. A. Bragg and A. D. Smith, *Org. Biomol. Chem.*, 2011, **9**, 559–570; (e) B. Hu, M. Meng, J. S. Fossey, W. Mo, X. Hu and W.-P. Deng, *Chem. Commun.*, 2011, **47**, 10632–10634; (f) Z. Wang, J. J. Ye, R. Wu, Y. Z. Liu, J. S. Fossey, J. G. Cheng and W. P. Deng, *Catal. Sci. Technol.*, 2014, **4**, 1909–1913.
- 7 J.-c. Meng, V. V. Fokin and M. G. Finn, *Tetrahedron Lett.*, 2005, **46**, 4543–4546.
- 8 (a) H. Nishiyama, M. Kondo, T. Nakamura and K. Itoh, *Organometallics*, 1991, **10**, 500–508; (b) D. A. Evans, J. A. Murry, P. Vonmatt, R. D. Norcross and S. J. Miller, *Angew. Chem., Int. Ed.*, 1995, **34**, 798–800.
- 9 Selectivity factor ( $s$ ) =  $\ln[(1 - c)(1 - ee)]/\ln[(1 - c)(1 + ee)]$  where  $c$  = conversion and the  $ee$  refers to that of the starting material.
- 10 M. K. Christensen, K. D. Erichsen, C. Trojel-Hansen, J. Tjornelund, S. J. Nielsen, K. Frydenvang, T. N. Johansen, B. Nielsen, M. Schested, P. B. Jensen, M. Ikaunieks, A. Zaichenko, E. Loza, I. Kalvinsh and F. Bjorkling, *J. Med. Chem.*, 2010, **53**, 7140–7145.
- 11 H. B. Rasmussen and J. K. MacLeod, *J. Nat. Prod.*, 1997, **60**, 1152–1154.
- 12 K. Monde, K. Sasaki, A. Shirata and M. Takasugi, *Phytochemistry*, 1991, **30**, 2915–2917.
- 13 K. Tchabanenko, N. S. Simpkins and L. Male, *Org. Lett.*, 2008, **10**, 4747–4750.
- 14 M. Panera, J. Díez, I. Merino, E. Rubio and M. P. Gamasa, *Inorg. Chem.*, 2009, **48**, 11147–11160.
- 15 (a) M. Ahlquist and V. V. Fokin, *Organometallics*, 2007, **26**, 4389–4391; (b) B. R. Buckley, S. E. Dann, D. P. Harris, H. Heaney and E. C. Stubbs, *Chem. Commun.*, 2010, **46**, 2274–2276; (c) B. R. Buckley, S. E. Dann and H. Heaney, *Chem. – Eur. J.*, 2010, **16**, 6278–6284; (d) B. T. Worrell, J. A. Malik and V. V. Fokin, *Science*, 2013, **340**, 457–460.
- 16 G.-C. Kuang, P. M. Guha, W. S. Brotherton, J. T. Simmons, L. A. Stanke, B. T. Nguyen, R. J. Clark and L. Zhu, *J. Am. Chem. Soc.*, 2011, **133**, 13984–14001.
- 17 (a) L. Jin, D. R. Tolentino, M. Melaimi and G. Bertrand, *Sci. Adv.*, 2015, **1**, DOI: 10.1126/sciadv.1500304; (b) A. Makarem, R. Berg, F. Rominger and B. F. Straub, *Angew. Chem., Int. Ed.*, 2015, **54**, 7431–7435.
- 18 B. R. Buckley and D. R. B. Fernandez, *Tetrahedron Lett.*, 2013, **54**, 843–846.
- 19 C. Abbadie, O. B. McManus, S.-Y. Sun, R. M. Bugianesi, G. Dai, R. J. Haedo, J. B. Herrington, G. J. Kaczorowski, M. M. Smith, A. M. Swensen, V. A. Warren, B. Williams, S. P. Arneric, C. Eduljee, T. P. Snutch, E. W. Tringham, N. Jochnowitz, A. Liang, D. Euan MacIntyre, E. McGowan, S. Mistry, V. V. White, S. B. Hoyt, C. London, K. A. Lyons, P. B. Bunting, S. Volksdorf and J. L. Duffy, *J. Pharmacol. Exp. Ther.*, 2010, **334**, 545–555.
- 20 A. D. Laird, P. Vajkoczy, L. K. Shawver, A. Thurnher, C. Liang, M. Mohammadi, J. Schlessinger, A. Ullrich, S. R. Hubbard, R. A. Blake, T. A. T. Fong, L. M. Strawn, L. Sun, C. Tang, R. Hawtin, F. Tang, N. Shenoy, K. P. Hirth, G. McMahon and J. M. Cherrington, *Cancer Res.*, 2000, **60**, 4152–4160.
- 21 (a) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758; (b) Y. Kamano, H.-p. Zhang, Y. Ichihara, H. Kizu, K. Komiyama and G. R. Pettit, *Tetrahedron Lett.*, 1995, **36**, 2783–2784; (c) A. Natarajan, Y. Guo, F. Harbinski, Y.-H. Fan, H. Chen, L. Luus, J. Diercks, H. Aktas, M. Chorev and J. A. Halperin, *J. Med. Chem.*, 2004, **47**, 4979–4982.
- 22 (a) M. M. M. Santos, *Tetrahedron*, 2014, **70**, 9735–9757; (b) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi and R. Nagata, *J. Med. Chem.*, 2001, **44**, 4641–4649.
- 23 (a) Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673–3682; (b) D. Tomita, K. Yamatsugu, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 6946–6948; (c) J.-S. Yu, F.-M. Liao, W.-M. Gao, K. Liao, R.-L. Zuo and J. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 7381–7385.
- 24 B. M. Trost, D. A. Bringley, T. Zhang and N. Cramer, *J. Am. Chem. Soc.*, 2013, **135**, 16720–16735.
- 25 C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363–5367.
- 26 (a) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2014, **114**, 1783–1826; (b) A. Fürstner, *Angew. Chem., Int. Ed.*, 2013, **52**, 2794–2819; (c) Y. Jiang, Y. Wei, X.-Y. Tang and M. Shi, *Chem. – Eur. J.*, 2015, **21**, 7675–7681.
- 27 Personal communication J. Zhou.
- 28 (a) G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.*, 2003, **103**, 3119–3154; (b) H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horiata, M. Kondo and K. Itoh, *Organometallics*, 1989, **8**, 846–848.
- 29 (a) G. J. Dawson, C. G. Frost and J. M. J. Williams, *Tetrahedron Lett.*, 1993, **34**, 3149–3150; (b) J. Sprinz and G. Helmchen, *Tetrahedron Lett.*, 1993, **34**, 1769–1772; (c) P. von Matt and A. Pfaltz, *Angew. Chem., Int. Ed.*, 1993, **32**, 566–568.
- 30 B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921–2944.
- 31 J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486–2528.
- 32 R. Noyori and H. Takaya, *Acc. Chem. Res.*, 1990, **23**, 345–350.
- 33 J. M. Brunel, *Chem. Rev.*, 2007, **107**, PR1–PR45.
- 34 Isolation of organic azides is potentially dangerous. Organic azides in pure forms especially with low molecular weights or C:N ratios < 2 can spontaneously explode. Extreme care should always be used when handling and isolating organic azides.
- 35 S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188–5240.
- 36 J. S. Fossey and W. D. G. Brittain, *Org. Chem. Front.*, 2015, **2**, 101–105.

